Pharmacotherapy Update

Spring 2011 Lebanon VAMC Pharmacy

Special points of interest:

- **Patient Safety Notice**: Is dronedarone (Multaq®) as safe as we thought?
- **Drug Review**: Read all about insulin degludec... a new long-acting insulin currently in clinical trials
- **Literature review**: Is the combination of sertraline and naltrexone effective for the treatment of depression and alcohol dependence?

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Editor Notes

Spring is upon us Lebanon VA!

Looks like the cold days of winter are behind us and spring has finally arrived. As the days become longer, find yourself a quiet spot outside to soak up the sun along with the latest in pharmacy news found right here in the pages of this issue's Pharmacotherapy Update.

First up, a formulary change regarding the use of topical metronidazole formulations is outlined. Next you will find a review of currently available insulin types with information about a new insulin possibly entering the market in the future.

As you read along, you will find a literature review discussing the effectiveness of sertraline in combination with naltrexone for the treatment of co-occurring depression and alcohol dependence.

Next, you will find the latest in drug safety. This section highlights the most recent changes made by the Food and Drug Administration (FDA) to the package labeling of dronedarone (Multaq®).

Lastly, is a review of the different bupropion formulations, which can be found in the drug information section.

Don't forget to enjoy the pharmacy fun section and get to know one of our pharmacists featured in the pharmacist's corner.

Read on and soak up the sun!

Kristie Wahl, Pharm.D. and Dina Hunsinger-Norris, Pharm.D., BCPS, Editors

Formulary Highlights: Topical Metronidazole

Topical metronidazole is currently commercially available as a gel and a cream. The gel is available as a 0.1% and 0.75% preparation. The cream is available as a 0.75% preparation only. The cost for these preparations is shown in the table below.

Preparation	Amount	Cost
0.75% gel	45 grams	$1.90
0.75% cream	45 grams	$8.33
1.0% gel	60 grams	$71.30

As a cost avoidance initiative, it has been decided by the Pharmacy & Therapeutics Committee, with the support of Dr. Toombs of Dermatology, to convert all patients on either the 1.0% gel or 0.75% cream over to the 0.75% gel. A letter was sent out to each veteran currently receiving the 1.0% gel or 0.75% cream, detailing the conversion.

The 0.75% cream and the 1.0% gel products will become local non-formulary agents, requiring the submission of a non-formulary request if use of the agents is felt to be required. Any questions regarding this matter may be directed towards Kevin Koons, Assistant Chief of Pharmacy.

Is there a new insulin on the block?

By: Monica Bowen, Pharm.D., PGY-2 Ambulatory Care Resident

Diabetes mellitus is a chronic disease that affects nearly 26 million people – about 8% of the United States population. It is the seventh leading cause of death in our country.[1] The CDC estimates that as many as 1 in 3 adults could have diabetes in 2050 if current trends continue.[2] Oral agents which lower blood glucose are typically utilized initially in patients with type 2 diabetes. A combination of 2-3 oral medications may be used in an effort to control hyperglycemia. However, since patients are living longer with the disease, many progress to the point of requiring insulin to be able to properly regulate blood glucose. Currently available insulin products include basal (long-acting) and bolus (short-acting) therapies. The basal insulins include NPH, insulin detemir (Levemir®), and insulin glargine (Lantus®). Duration of action for these agents are approximately 10-24 hours, up to 24 hours, and 24 hours, respectively.[3]

Insulin degludec is an experimental insulin analog which is being studied in both type 1 and type 2 diabetes mellitus. It is currently in phase 3 trials. Insulin degludec is an ultra-long acting insulin, which forms soluble multihexamers at the injection site, allowing gradual absorption, resulting in a peakless pharmacokinetic profile at steady state. The multihexamer design is similar to that of insulin glargine, and contrasts with insulin detemir, which binds to albumin and thus allows for delayed absorption.[3] Proposed advantages over current insulin formulations include lower risk of hypoglycemia, less injections (with a 3 times/week dosing strategy), and the option to mix with bolus insulin in the same syringe.

In March, a phase 2 study comparing insulin degludec with insulin glargine was published.[4] The study compared 3-times weekly insulin degludec, once daily insulin degludec, and once daily insulin glargine. Patients had type 2 diabetes, were insulin-naïve, and were eligible for randomization if they were taking at least 1500mg per day of metformin and the median before-breakfast SMBG value was 136 mg/dl or more at the end of the pre-randomization period.

Dosing was 10 units for the once daily regimens and 20 units for the 3 times weekly insulin degludec regimen. Participants were titrated weekly to a target fasting blood glucose of 72-108 mg/dL. After 16 weeks, there was no significant difference between treatment groups in terms of A1c and fasting plasma glucose; A1c reduction was between 1.3-1.5% for all treatment groups. Rates of hypoglycemia also did not differ between groups. There were two serious adverse events reported, which were not thought to be related to the study drug.

The authors concluded that a 3 times per week, weekend-off, dosing regimen might appeal to some patients and may potentially help with acceptance and early initiation of insulin therapy. However, adherence to this type of regimen may be difficult. It should be noted that the study was funded by Novo Nordisk, manufacturer of insulin degludec, and three of the primary authors were Novo Nordisk employees who were involved in all aspects of the study.

Based on the results of this study, insulin degludec appears to be similar in terms of safety and efficacy to insulin glargine. However, this study aimed to estimate a treatment difference in A1c rather than determining superiority or non-inferiority. The BEGIN study, which is currently underway, is evaluating the change in A1c after switching from insulin glargine to insulin degludec and may give further insight into its place in therapy.[5] Insulin degludec was also studied with a "bolus boost" of insulin aspart, and compared to insulin glargine. This small study found that insulin degludec plus insulin aspart was safe and similarly effective as insulin glargine.[6] Further study in a larger phase 3 trial is warranted in order to determine insulin degludec's optimum use and place in therapy.

References:
1. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf
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3. Clinical Pharmacology [database on the internet] Tampa (FL): Gold Standard Multimedia, Inc. [cited 2011 Apr 20]. Updated periodically.
4. Zinman B, Fulcher G, Rao PV, et al. Insulin degludec, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomized, open-label, phase 2 trial. Lancet 2011;377:924-31.
5. http://clinicaltrials.gov/ct2/results?term=degludec
6. Heise T, Tack CJ, Cuddihy R, et al. A new-generation ultra-long-acting basal insulin with a bolus boost compared with insulin glargine in insulin-naïve people with type 2 diabetes. Diabetes Care 2011;34:669-74.

DID YOU KNOW...

The popular drink '7-Up' was originally a version of a "lithiated" patient medicine, containing small amounts of lithium. Ironically, it was introduced to the U.S. markets in the 1930s - during the time of the Great Depression!

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Sertraline and naltrexone for the treatment of co-occurring depression and alcohol dependence… does it work?

By: Emily Herman, Philadelphia College of Pharmacy Pharm.D. Candidate

There is little evidence for the use of antidepressants in patients with co-occurring depression and alcohol dependence. Furthermore, the few clinical trials that have studied the use of antidepressants in this patient population report contradictory results. These trials suggest that antidepressant monotherapy has mild to moderate effect on alleviating depression, but has little effect on reducing the amount of alcohol intake. Because there is a strong correlation between depression and alcohol dependence, it is important to treat both conditions to achieve a positive outcome.

The present fourteen week randomized, double-blind, placebo-controlled clinical trial took place at the University of Pennsylvania Treatment Research Center. The trial was funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The objective of the study was to evaluate the efficacy and safety of combination treatment with sertraline and naltrexone in treating patients with both depression and alcohol dependence. Subjects were enrolled in the study if they consumed 12 or more alcoholic drinks per week, consumed alcohol on at least 40% of the 90 days before treatment, and scored a 10 or higher on the Hamilton Depression Rating Scale (HAM-D) indicating at least mild depression. Subjects were also required to be abstinent from alcohol on the three days prior to treatment. Individuals were not included in the study if they were diagnosed with bipolar affective disorder, schizophrenia, an organic mental disorder, substance dependence or a severe medical illness. Individuals taking an antidepressant regularly or a psychiatric medication other than an antidepressant were also excluded from the trial.

170 subjects were randomized into four groups and were treated with either sertraline plus naltrexone, sertraline monotherapy, naltrexone monotherapy or placebo. Subjects were titrated to 100mg of naltrexone and 200mg of sertraline as tolerated. The doses in this trial were specifically chosen to reflect effective doses from other trials studying naltrexone or sertraline for the treatment of their respective conditions. All subjects attended cognitive behavioral therapy (CBT) sessions. The primary drinking outcomes measured total abstinence and time to relapse to heavy drinking throughout the treatment period. Secondary drinking outcomes of time to relapse to any drinking and percentage of subjects not drinking heavily were utilized to support the primary outcomes. The primary depression outcomes measured HAM-D assessment scores and the percentage of subjects not depressed at the end of the study with a HAM-D score of 9 or less. The trial had an 80% power and $\alpha = 0.01$.

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Multiple Safety Concerns with Multaq®

By: Kristie Wahl, Pharm.D., PGY-1 Pharmacy Practice Resident

Dronedarone (Multaq®) is very similar to amiodarone, one difference being it lacks an iodine moiety. It was approved by the FDA in 2009 for the prevention of atrial fibrillation (AF). However, data has shown that it is less effective than amiodarone. Specifically, the DIONYSOS trial showed that in patients with persistent atrial fibrillation, dronedarone was less effective than amiodarone in decreasing AF recurrence but it was better tolerated. Dronedarone is also contraindicated in patients with NYHA class IV heart failure because of the results of the ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease) trial. This study showed that in patients receiving dronedarone, there was an increased mortality associated with progression of heart failure. In general, the major adverse cardiac effects of dronedarone are bradycardia and QT prolongation. Like amiodarone, dronedarone inhibits renal tubular secretion of creatinine, which can increase plasma creatinine levels without a reduction in GFR. Furthermore, dronedarone increases digoxin levels. It does not, however, appear to alter the INR when used with warfarin. It appears dronedarone lacks the more serious adverse effects seen with amiodarone, such as pulmonary injury, hyper- or hypothyroidism, hepatic and renal toxicity, dermatologic reactions, and visual impairment[1].

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Did you know…

Caleb Bradham, a pharmacist from New Bern, NC, created a carbonated beverage, named Brad's Drink, to sell to fountain customers in his pharmacy. He deemed his drink "Exhilarating, invigorating and aids digestion." In 1898 Brad's Drink was renamed Pepsi-Cola.

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The study primarily consisted of middle-aged Caucasian men with 75% of subjects reporting a family history of substance abuse problems and 50% of subjects reporting a family history of depression. The average HAM-D score for all subjects was 23.1 indicating that most subjects were severely depressed at baseline. The results of the primary drinking outcomes found that subjects taking both sertraline and naltrexone had a 53.7% total abstinence rate when compared to a total abstinence rate of 23.8% for the other three groups combined ($p = 0.001$). Also, the combination group experienced an average period of 63.6 days (median = 98 days) before relapsing to heavy drinking when compared to an average of 42.4 days (median = 26 days) for the other three groups combined ($p = 0.003$). Secondary drinking outcomes were also significantly improved in subjects taking combination treatment. Primary depression outcomes were not statistically significant between groups; however, 83.3% of patients taking both sertraline and naltrexone were no longer depressed compared to 58.3% of patients in the other three groups at the end of the treatment period ($p = 0.014$). There were no significant group differences in reports of adverse events.

The strengths of the clinical trial were the use of appropriate statistical tests and the criteria resulting in the inclusion or exclusion of subjects. Also, the trial was randomized, double-blinded and placebo-controlled. Some limitations of the trial were that it took place at a single center and the effect of CBT on depression and alcohol abstinence is unknown. It is also difficult to generalize the results of the study to a larger population due to the high percentage of middle-aged Caucasian male subjects. The efficacy and safety of long-term combination therapy is not established.

The authors concluded that more subjects receiving combination therapy of sertraline and naltrexone were able to achieve abstinence and delay relapse when compared to subjects receiving monotherapy or placebo. Less subjects receiving combination therapy were depressed at the end of the treatment period; however, this result did not reach statistical significance when compared to subjects taking monotherapy or placebo. More studies are necessary to verify the outcomes of the present study and to determine long-term efficacy and safety of the combination of sertraline and naltrexone for co-occurring depression and alcohol dependence.

References:

1. Anton RF, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: a randomized controlled trial. *JAMA* 2006;295:2003-17.
2. Nunes EV, et al. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. *JAMA* 2004;291:1887-96.
3. Pettinati HM, et al. A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. *Am J Psychiatry* 2010; 167:668-75.
4. Pettinati HM, et al. Antidepressant treatment of co-occurring depression and alcohol depressed dependence. *Biol Psychiatry* 2004;56:785-92.

DID YOU KNOW...

In 1888, Atlanta pharmacist John S. Pemberton developed an "Esteemed Brain Tonic and Intellectual Beverage," which contained: caffeine, "secret" ingredients, and cocaine. Modified for today's taste (and laws), the product is a staple, billion-dollar seller. What was Pemberton's concoction? None other than Coca-Cola.

Pharmacy Fun: laughter is the best medicine…

A distraught patient phoned her doctor's office. Was it true, the woman wanted to know, that the medication the doctor had prescribed was for the rest of her life? She was told that it was. There was a moment of silence before the woman continued, "I'm wondering, then, just how serious my condition is. This prescription is marked: "NO REFILLS."

A pharmacist is going over the directions on a prescription bottle with an elderly patient. "Be sure not to take this more often than every 4 hours," the pharmacist says. "Don't worry," replies the patient. "It takes me 4 hours to get the lid off".

"Laughter is the best medicine, but your insurance only covers chuckles, snickers and giggles."

Define miracle drug?
Answer - A miracle drug is one that stayed the same price as last year.

Continued from page 3: safety concerns with dronedarone

However, there have been several changes made to the product labeling in 2011 given that in its first year on the market, over 400 serious adverse event reports in North America have linked dronedarone to worsening arrhythmias, drug-drug interactions, heart failure, kidney failure, and liver failure. The table below outlines the potential safety issues with dronedarone.[2,3]

Safety Concerns	Recommendation
Liver failure Acute failure requiring transplant	Patients should be warned about the signs and symptoms of liver injury (e.g. nausea, vomiting, dark urine, itching, jaundice, malaise). Monitor liver enzymes periodically, especially within the first 6 months after drug initiation. At this time, it is not known if routine LFT monitoring will minimize the risk of severe liver injury.
Heart failure New onset or worsening	Advise patients to consult a physician if they develop signs or symptoms of heart failure (e.g. weight gain, dependent edema, increasing shortness of breath). If heart failure develops or worsens, consider suspension or discontinuation of dronedarone.
Drug interaction Warfarin, increased INR	Dronedarone moderately inhibits CYP3A4 and CYP2D6, leading to increased concentrations of warfarin. Labeling changed to reflect increased INR with or without bleeding events seen in patients initiated on dronedarone. INR should be monitored after initiating dronedarone in patients taking warfarin.

Where is dronedarone's place in therapy? The latest update of the 2006 atrial fibrillation treatment guidelines from ACCF/AHA/HRS, published in January 2011, recommends dronedarone over amiodarone in the following patients[1]:

- Those with no or minimal heart disease
- Those with hypertension without substantial left ventricular hypertrophy
- Those with coronary artery disease

Dronedarone should not be used in patients with class IV heart failure or for patients who have had an episode of decompensated heart failure within the past four weeks, especially with left ventricular ejection fraction ≤35%[3].

Remember, continue to report any adverse events related to dronedarone. These can be reported by calling the FDA MedWatch program at 1-800-FDA-1088 or by completing a form available online at www.fda.gov/medwatch/report/hcp.htm.

References:
1. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline): A Report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.* 2011;57;223-242.
2. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm243762.htm.
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Drug Information: What is the difference between bupropion formulations?

By: Ross Coder, Pharm.D. Candidate 2011, Kristie Wahl, Pharm.D., PGY-1 Pharmacy Resident

Bupropion is currently available as generic bupropion as well as bupropion marketed under the brand names Wellbutrin SR and Wellbutrin XL. It is also available as two different salt formulations; hydrochloride (HCl) and hydrobromide (HBr). Only bupropion HCl will be discussed here.

Bupropion was first developed to provide a better safety and tolerability profile of existing antidepressants. It has a dual effect on norepinephrine and dopamine systems. It was first marketed as an immediate-release (IR) product first introduced in 1989. This formulation required multiple daily dosing (three times daily) for the treatment of major depressive disorder (MDD). The dosing schedule proved inconvenient for patients and resulted in a greater frequency of noncompliance[1]. This prompted the development of longer acting products. In 1996, a sustained-release (SR or SA) formulation became available. Bupropion SR still required multiple daily doses (two times a day). With other antidepressants offering once-daily dosing, the makers of bupropion decided to create a once-daily extended-release (XL) formulation also, which became available in 2003[1].

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Did you know…

Hubert H. Humphrey served as the Mayor of Minneapolis, a U. S. senator and the vice president of the United States under President Lyndon B. Johnson. His long political career came after Humphrey had a brief career as a pharmacist in his dad's drugstore .

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Continued from page 5: keeping bupropion formulations straight

To make things even more confusing, some of the formulations have gone generic. When generic, some are marketed under the drug name bupropion while others fall under "branded generic" names.

All three formulations have similar side effect profiles with xerostomia, headache, agitation, insomnia, tremor, and nausea being the most common. The XL and SR formulations are usually more tolerable than the immediate release formulation[1]. Bupropion appears to have among the lowest incidence of sexual dysfunction, weight gain, and somnolence. Below is a table outlining the variations in the different bupropion formulations[2,3,4].

Formulation	Brand Names	Starting Dose	Usual Dosing Schedule	Generic (Y/N)	Formulary Status
Bupropion HCl Immediate Release (IR) - Approved for MDD	Wellbutrin	100 mg twice daily	Dosed up to three times daily, max dose 450 mg/day	Y	Formulary
Bupropion HCl Sustained Release (SR or SA) - Approved for MDD	Wellbutrin SR, Budeprion SR (branded generic)	150 mg daily	Dosed twice daily, max dose 400 mg/day	Y	Formulary
Bupropion HCl Sustained Release (SR or SA) - Approved for smoking cessation only	Zyban, Buproban (branded generic)	150 mg daily	Dosed once daily, max dose 450 mg/day	Y	Formulary
Bupropion HCl Extended Release (XL) - Approved for MDD & SAD	Wellbutrin XL, Budeprion XL (branded generic)	150 mg daily	Dosed once daily, max dose 450 mg/day	Y	Non-formulary

HCl = hydrochloride, HBr = hydrobromide, MDD = major depressive disorder, SAD = seasonal affective disorder

There is room for error with the availability of multiple preparations as outlined above. It is also important to remember the dosing is different when the once daily bupropion hydroBROMIDE formulation is used (174 mg bupropion HBr = 150 mg bupropion HCl). When in doubt, don't be afraid to ask a pharmacist! Note that a Medication Guide must be dispensed with each bupropion prescription.

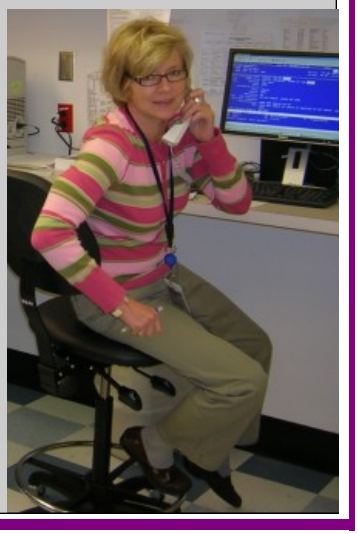
References:
1. Fava M, Rush AH, Thase ME, et al. 15 Years of Clinical Experience With Bupropion HCl: From Bupropion to Bupropion SR to Bupropion XL. *J Clin Psychiatry*. 2005;7:106-113.
2. Wellbutrin XL. [package insert] Research Triangle Park, NC GlaxoSmithKline;2008.
3. Wellbutrin SR. [package insert] Research Triangle Park, NC GlaxoSmithKline;2010.
4. Bupropion. *Drug Facts and Comparisons.* Facts & Comparisons® eAnswers [online]. 2009. Available from Wolters Kluwer Health, Inc. Accessed March 31, 2011.

Pharmacist Corner

Featuring: Grazyna Prokopczyk, MSc, PhD

Education: Grazyna completed her studies at the University of Warsaw-Poland, earning the degrees listed below:

- Faculty of Pharmaceutical Sciences MSc (Master of Science) 1972
- Faculty of Pharmaceutical Sciences, PhD 1978



Work experience: Grazyna has worked in the following hospitals in New York state as a pharmacist:

- Hudson Valley VA**,** Mt. Kisco Medical Center, & Putnam Hospital

Duties here at the VA: Grazyna rotates through the inpatient, outpatient, and chemotherapy pharmacies. She also rounds with the medical team on the hospice unit.

Fun Facts:

1) Grazyna was this year's Pharmacy Department winner of the NCAA men's basketball tournament bracket prediction. She won without having followed the teams!
2) She lived in Nigeria, Africa for 5 years

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